**REMARKS**

Claims 16-17 and 21-28 are pending in this application. Claims 16-17 and 21-28 have been rejected. Claim 16 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested.

**I. Claim Objections**

Claim 16 is objected to because the term "BCRP" is not spelled out the first time it appears in the claims. Claim 16 has been amended to recite Breast Cancer Resistance Protein (BCRP), in accordance with the Examiner's suggestion. Withdrawal of this objection is, therefore, respectfully requested.

**II. Written Description Requirement**

Claims 16, 17, 21-28 have been rejected under 35 U.S.C. 112 first paragraph as failing to comply with the written description requirement. It is suggested that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed had possession of the claimed invention. The Examiner has suggested that the claims are directed to an isolated antibody that recognizes an extracellular portion of a BCRP and wherein the

extracellular portion of the BCRP is in its natural conformation. It is suggested that given the broadest reasonable interpretation, the claims embrace a genus encompassing a large number of antibodies recognizing different epitopes of the extracellular portion of the BCRP in its natural conformation, wherein for each epitope the antibodies could be monoclonal, polyclonal, chimeric or humanized. The specification is suggested to fail to provide adequate disclosure for the genus in terms of distinguishing characteristics. It is suggested that the specification fails to disclose even one such antibody by its sequence structure, and therefore fails to provide an adequate description to teach the structures and the identifying characteristics of the genus of antibodies encompassed by the claims and further that the specification fails to teach the structure/function relationship with respect to antibodies that only recognize the external epitope of a BCRP that is in its natural conformation. Applicants respectfully traverse this rejection.

The Examiner appears to be requiring a description of the physical structure of the claimed antibodies in order to satisfy the written description requirement. However, antibodies have long been described and characterized by those of skill in the art in both the patent and scientific literature, by the antigens

which they recognize rather than their physical structure. This is wholly different than genes and proteins which are commonly described by their physical structure. Therefore, it is clear that a description of the physical structure of a claimed antibody is not necessary to convey to the skilled artisan that the applicant has possession of such an antibody. Instead a description of the antigen which the antibody binds is the commonly accepted way of describing an antibody or class of antibodies and meets the written description requirement.

In the present case Applicants have described the antigen recognized by the claimed antibodies in terms of its natural conformation and location on the outside of the cell. This description is easily understood and useful to those of skill in the art, whereas a recitation of the amino acid sequence of this antigen would do little to enhance the skilled artisan's understanding of what is recognized by the claimed antibodies.

The presently claimed antibodies were not raised against, and would not be expected to recognize, an isolated peptide representing the extracelluar domain of BCRP. Instead, they were raised against the extracellular domain of the BCRP protein as it naturally occurs as described in the specification. Viewed in this context, it is clear that the description provided in the

specification is an effective way of describing the claimed antibodies from the perspective of the skilled artisan.

Numerous examples of patent and scientific literature exist where an antibody is described or claimed without a description of its physical structure. In particular, U.S. Patent 5,994,088 (Mechetner) cited by the Examiner in the present office action claims methods for using antibodies to an ABC transporter but does not provide a physical description of such antibodies. Also, the art describes BCRP antibodies without providing the physical structure of such an antibody. For example, Zhou, S. et al., "The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side population phenotype", Nature Medicine 7(9):1028-1034 (2001) [PTO -1449 reference BY]; Abbott, B.L. et al. "Low levels of ABCG2 expression in adult AML blast samples", Blood 100(13):4594-4601 (2002); Scheffer, G.L. et al. "Breast Cancer Resistance Protein is localized at the plasma membrane in Mitoxanthrone- and Topotecan-resistant cell lines, Cancer Res. 60:2589-2593 (2000) provided with March 4, 2003 Office action response; U.S. Patent No 6,313,277 (Ross; PTO-1449 Reference No. C); U.S. Application No. 09/961,086 (Ross) is being used to prosecute following BCRP antibody claims as follows: Claim 5. An antibody which binds to the protein of claim 1 [Claim 1 reads "Breast Cancer

Resistance Protein which induces resistance to cancer chemotherapeutic drugs, or fragments or derivatives thereof].; Claim 6. The antibody of claim 5 which is monoclonal.; Claim 7. The antibody if claim 5 which is polyclonal.

Thus, Applicants believe that the present invention is adequately described in the specification to satisfy the written description requirement under 35 U.S.C. 112, first paragraph and respectfully request withdrawal of this rejection.

**III. Enablement Rejection**

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and/or use the invention.

The Examiner further suggests that the specification fails to teach what is now claimed as it relies on the functional ability of an antibody to determine whether it detects a protein in its natural conformation and that one of skill could not practice the invention without undue experimentation.

Applicants respectfully disagree with the Examiner's analysis and conclusion. There are sufficient teachings in the present application for generating the claimed antibodies, e.g.,

at page 39 of the specification, a human BCRP cDNA (obtained as a full length EST) was cloned into a Harvey murine sarcoma virus backbone to create the HaBCRP retroviral vector. This vector was introduced into the ecotropic packaging cell line GPE86 and vector-containing supernatant was used to transduce NIH 3T3 cells. A polyclonal population of cells (designated 3T3-BCRP) was isolated by flow cytometry, gating on cells that efflux the fluorescent dye Hoechst 33342. Expression of the HuBCRP gene product in these cells was confirmed by Western blot analysis, see page 39, lines 4-10. The 3T3-BCRP cells were used to immunize mice, see specification at page 39, line 11. Individual mice that showed antibody reactivity in the serum were killed and hybridoma clones were isolated after cell fusion and selection. Supernatants from each hybridoma clone were screened by flow cytometry using a human breast cancer cell line (MCF-7) that had been transduced with an amphotrophic HaBCRP vector, see specification at page 39, lines 15-19. Any supernatant that showed reactivity in this assay was then back-screened on the parental MCF-7 line and clones that reacted with the MCF-7 HaBCRP cells but not with the parental MCF-7 line were scored as positive and specific. These cells were subcloned and re-screened based on the indicator cell lines, see Figure 1, and specification at page 39, lines 19-24. Independent subclones

that showed relatively large shifts with the MCF-7 HaBCRP cells, but not with the parental control cells were then isolated. Clones that detected expression of the HaBCRP vector in bone marrow cells from previously transplanted mice were expanded to produce larger quantities of supernatant *ex vivo* with a rollerbottle production system, see specification at page 39, lines 25-29. The antibodies were then purified on an affinity column. These antibodies were then tested for their ability to detect the endogenously expressed huBCRP gene product in human umbilical cord blood samples. Efficient and high expression of the antibodies was achieved.

Further, the Zhou and Abbott references (cited above) describe an antibody designated 5D3, that recognizes an external epitope of the BCRP protein in its natural conformation. The 5D3 antibody was generated by Dr. Sorrentino along with three other independent monoclonal antibodies that recognize an external epitope of the BCRP protein in its natural conformation (7A3, 1C5, and 8C2) using the methodology described in the specification. Given this success, Applicants do not understand why the Examiner doubts the ability of skilled artisans to use this same methodology to generate additional antibodies within the scope of the claims.

The Examiner also suggests that the detection of BCRP expression in living cells is not sufficient evidence that the antibody made by the inventors recognizes an external epitope of BCRP in its natural conformation. However, no rationale for finding this evidence insufficient is provided. Rather, the Niman patent is cited for reasons which do not appear relevant to the question of enablement. Further explanation of the basis of this assertion and the relevance of the Niman patent to this enablement issue is needed for Applicants to respond.

**IV. Indefiniteness Rejection**

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that the term "natural conformation" is unclear in the context of the claims, and thus the metes and bounds are unclear. Applicants respectfully disagree.

The term "natural conformation" has appeared in the claims since this application was filed on May 29, 2001.

The term "natural conformation" refers to the BCRP protein as it naturally exists on the surface of a cell. This is clear from the description of antibodies provided in the specification

at page 9, lines 21-29 and in the description of the process used to generate and characterize such antibodies found on pages 20-24. Therefore, the requirement of § 112, second paragraph, are met.

**V. Obviousness**

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ross et al. (U.S. 6,313,277) in view of Mechetner et al. (U.S. 5,994,088).

It is suggested that Ross et al. teach the BCRP protein as well as the cDNA encoding such protein and state that it is an objective of the invention to provide antibodies to the BCRP. Ross et al. teach that the monoclonal antibody could be prepared by the numerous methods known in the art, such as immunizing a mammal with a BCRP protein or immunizing a mammal with a whole cell with the antigen of interest on its surface and subsequently producing hybridoma secreting such antibody with spleen cells of the immunized mice. It is acknowledged that Ross et al. do not teach making an antibody that recognizes the extracellular epitope in its natural conformation.

It is suggested, however, that Mechetner et al. teach a method of making antibodies that would bind to the extracellular portion of another ABC transporter protein, P-glycoprotein (Pgp)

in its natural conformation. It is suggested that Mechetner et al. teach that several of such antibodies recognizing the extracellular portion of the Pgp are known in the art,(such as the 4E3 mAb as taught by Arcesi et al.) that does not disrupt drug efflux, and UIC2 that inhibit Pgp-mediated drug efflux (column 4, lines 30-65 and column 6, lines 19-46), wherein they clearly teach that the UIC2 recognizes the extracellular portion of the Pgp in its biochemical conformation (natural conformation). It is further suggested that Mechetner et al. teach methods of making such antibody, i.e. transfecting balb/c 3T3 fibroblasts with a vector comprising and expressing the cDNA of Pgp immunizing syngeneic mice with selected cells expressing high levels of Pgp and producing hybridomas using spleen cells of the immunized mice and selecting for antibodies of interest. It is also suggested that Mechetner et al. teach that the method could be used for producing monoclonal or polyclonal, chimeric or humanized antibodies. The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method as taught by Mechetner in making an antibody that binds to the extracellular epitope of BCRP in its natural conformation with a reasonable expectation of success. The Examiner suggests, that given the method known in the art, and given the knowledge regarding the importance of the

extracellular portion of an ABC transporter protein, and given the cDNA of BCRP provided by Ross et al, it is within the knowledge of the skilled artisan to make a similar antibody as 4E3 or UIC2 that binds to the extracellular epitope of BCRP in its natural conformation. The Examiner suggests that the present invention as a whole is prima facie obvious in the absence of evidence to the contrary. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

The cited references fail to meet all of these criteria with respect to the claimed invention. Contrary to the Examiner's suggestion, one of skill would not have had any reasonable expectation of successfully identifying an antibody to a small domain target, such as the extracellular epitope of BCRP in its natural conformation, using the prior art methods.

The Mechetner patent describes the generation of an antibody that recognizes an extracellular epitope of the ABC transporter

P-glycoprotein. Mechetner does not overcome the general uncertainty in the prior art when it comes to the ability to generate antibodies that will recognize the extracellular portion of the ABC transporters. For most of these transporters, antibodies recognizing their extracellular portion have not been made despite the clear utility of such antibodies for recognizing these transporters in their natural conformation. Thus, the Mechetner patent does not change the basic point made in Dr. Sarkadi's previously submitted expert declaration. The generation of antibodies to extracellular portions of ABC transporters using conventional techniques is an uncertain exercise that cannot reasonably be expected to be successful before it is accomplished. Neither Ross nor Mechetner alone or combined teach the effective generation of isolated antibodies to ABC transporters in a natural conformation. Neither cited prior art reference provides any reasonable expectation of success in achieving the present invention. Thus, the present invention cannot be deemed to be obvious under 35 U.S.C. 103(a).

Withdrawal of this rejection is respectfully requested.

**Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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